Nonprescription Sunscreen Drug Products—Content and Format of Data Submissions To Support a GRASE Determination Under the Sunscreen Innovation Act

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Kristen Hardin at 240-402-4246.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2015
OTC

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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Nonprescription Sunscreen Drug Products—Content and Format of Data Submissions To Support a GRASE Determination Under the Sunscreen Innovation Act

Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance listed on the title page.

I. INTRODUCTION

This draft guidance addresses the current thinking of the Food and Drug Administration (FDA or Agency) on the format and content of information provided to support a request submitted under section 586A (586A request) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360fff-1), as amended by the Sunscreen Innovation Act (SIA),[2] or in support of a pending request as defined under section 586(6) of the FD&C Act (21 U.S.C. 360fff(6)).[3] A 586A request seeks a determination from FDA of whether an over-the-counter (OTC or nonprescription) sunscreen active ingredient,[4] or a combination of nonprescription sunscreen active ingredients,[5] is generally recognized as safe and effective (GRASE) for use under specified conditions and should be included in the OTC sunscreen drug monograph (GRASE determination). The GRASE determination is primarily based on FDA's review of safety and effectiveness data and other information submitted by the request's sponsor[6] (GRASE data

[1] This guidance has been prepared by the Division of Nonprescription Drug Products and the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] 21 U.S.C. Ch. 9 Sub. 5 Part I, enacted November 26, 2014.

[3] The SIA defines a "pending request" to mean a request for a nonprescription sunscreen active ingredient to be included in the over-the-counter monograph that was originally submitted as a time and extent application under section 330.14 of FDA's regulations (21 CFR § 330.14) and was determined to be eligible for review and for which safety and effectiveness data were submitted prior to the enactment of the SIA (section 586(6) of the FD&C Act).

[4] A "sunscreen," as defined in the SIA, means a drug containing one or more sunscreen active ingredients (section 586(9) of the FD&C Act (21 U.S.C. 360fff(9))), and the term "sunscreen active ingredient," as also defined in the SIA, means an active ingredient that is intended for application to the skin of humans for purposes of absorbing, reflecting, or scattering ultraviolet radiation (section 586(10) of the FD&C Act (21 U.S.C. 360fff(10))).

[5] For convenience, references in this guidance to an "active ingredient" also apply to combinations of active ingredients.

[6] An SIA "sponsor" is a person who has submitted a 586A request, a pending request, or any other application subject to the SIA (section 586(8) of the FD&C Act (21 U.S.C. 360fff(8))).

submission) as well as information and views submitted to the public docket by other interested parties.[7] Before that review may begin, however, FDA must review the GRASE data submission for completeness and determine accordingly whether to file or refuse to file it for substantive review (filing determination). If the submission is not sufficiently complete to enable us to conduct a substantive GRASE review, including being formatted in a manner that will enable us to evaluate its completeness, we will refuse to file the submission.[8]

We are issuing this draft guidance as directed by the SIA, which calls for FDA to publish a draft and final guidance on the format and content of information submitted by a sponsor in support of a 586A request or a pending request. When final, the recommendations in this draft guidance will help sponsors prepare GRASE data submissions for 586A requests[9] that are sufficiently complete to be filed for substantive review, as well as helping guide FDA's filing determinations. Only data submissions provided by or on behalf of a sponsor are subject to a filing determination as described in this draft guidance, and we anticipate that information provided by other interested parties will supplement the sponsor's data submission rather than duplicating the full extent of a complete data submission as described in this draft guidance. However, we encourage other interested parties to follow the recommendations in this guidance to the extent that they are applicable to a given submission. We also anticipate that the advice in this draft guidance will also be useful to persons who are preparing safety and efficacy data submissions for review by FDA in other regulatory proceedings whose intent is to determine whether particular nonprescription drug active ingredients or other OTC conditions are GRASE and therefore may be included in an applicable OTC monograph (such as a future non-sunscreen TEA (Time and Extent Application) or a request for additional data in an ongoing SIA proceeding).

Section II of this draft guidance provides background information on the sunscreen OTC monograph process and the new procedures governing GRASE determinations under the SIA (the SIA process). Section II also summarizes the filing determination process for GRASE data submissions and describes what sponsors can do if FDA refuses to file a GRASE data submission. Section III describes FDA's current thinking on the recommended format and content of a GRASE data submission that will be considered complete and therefore fileable for substantive review.

[7] Section 586B(b)(1) of the FD&C Act (21 U.S.C. 360fff-2(b)(1)).

[8] Section 586B(b)(2) of the FD&C Act (21 U.S.C. 360fff-2(b)(2)).

[9] We note that although the SIA directs FDA to issue a draft guidance on the format and content of information submitted by a sponsor in support of 586A and pending requests, pending requests were submitted prior to enactment of the SIA and thus not required to meet the filing requirements in the SIA at the time of their submission. The SIA exempts pending requests from the filing determination stage and provides that the FDA will issue a proposed sunscreen order based on the safety and effectiveness data submitted soon after enactment of the SIA (see section 586C(b)(2), (3), (4), and (5) (21 U.S.C. 360fff-3(b)(2), (3), (4), and (5))). There are eight pending requests, and, as required by the SIA, all of them have received proposed sunscreen orders. We recommend that any future data submissions regarding the eight pending requests follow the content and format recommendations outlined in this draft guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Regulation of Sunscreen Products[10]

All sunscreens are regulated as drugs in the United States under one of two processes:

- The new drug approval process described in 21 CFR part 314
- The OTC drug monograph process (also known as the OTC Drug Review) described in part 330 (21 CFR part 330), as supplemented by the SIA

Products regulated under the new drug approval process may not be marketed without FDA's prior review and approval of a new drug application (NDA) or abbreviated new drug application (ANDA) for each product. Products marketed under the OTC drug monograph process are not individually reviewed and approved prior to marketing. Instead, OTC drug monographs categorize drugs by therapeutic categories, such as sunscreens. For each category, the monograph establishes conditions under which any drug that satisfies those conditions and FDA's general regulations for OTC drugs is considered to be GRASE and not misbranded when used under the conditions prescribed, recommended, or suggested in labeling.[11]

Initially, active ingredients that were not used in sunscreens in the United States prior to the inception of the OTC Drug Review were not eligible for the OTC Drug Review. FDA considered a drug that was ineligible for inclusion in the OTC monograph system to be subject to the new drug approval process.

In 2002, before the SIA was enacted, FDA published the "time and extent application" (TEA) regulation in 21 CFR 330.14. The TEA regulation (§ 330.14(c)) established a process through which any person could request that an active ingredient or other OTC drug condition, including one not previously marketed in the United States before the inception of the OTC Drug Review, be added to an existing OTC drug monograph.

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[10] We have previously published *Federal Register* notices about rulemaking actions for OTC sunscreen monograph products and about actions taken under the SIA. This information can be found on our "Status of OTC Rulemakings" Web site (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/default.htm) and "Sunscreens" Web site (http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm).

[11] Part 330.

For OTC sunscreens, the SIA process supplements the TEA regulation. The SIA amended the FD&C Act in part by providing new procedures for establishing that nonprescription sunscreen active ingredients or combinations of nonprescription sunscreen active ingredients are GRASE and not misbranded when used under the conditions specified in a final sunscreen order.[12] Active ingredients that are determined to be GRASE in a final sunscreen order may be used in U.S.-marketed sunscreens without first obtaining an approved NDA or ANDA. Because the monograph and SIA processes are public, anyone, not just the sponsor who originated the request, may submit data during public comment periods.

As with the TEA process, the SIA process calls for an initial eligibility determination,[13] followed by submissions of safety and efficacy data, and a GRASE determination phase. However, the SIA process also requires FDA to make a filing determination as described in this draft guidance, and to make proposed and final GRASE determinations in the form of administrative orders rather than the rulemaking required by the TEA regulation. The SIA process also establishes strict timelines for the necessary administrative actions.

B. FDA'S Filing Determinations and Refusal To File a Request

The SIA requires FDA to conduct an initial filing review to determine whether a sponsor's submission of safety and efficacy data and other relevant information to support a 586A request for a sunscreen active ingredient is sufficiently complete to enable us to conduct a substantive GRASE review (including being organized so that we can determine its completeness).[14] The initial filing review will help conserve FDA resources and streamline the GRASE review for nonprescription sunscreen active ingredients by making the start of the GRASE review contingent on a determination that the submission is sufficiently complete to support a GRASE substantive review. As a result, it is the date of filing by FDA, and not the date when the submission was submitted to or received by FDA, that triggers FDA's statutory time frame for completing the GRASE determination and issuing a proposed sunscreen order (which in turn triggers various other action dates under the SIA).[15]

No later than 60 days after receiving a sponsor's GRASE data submission, FDA must take one of the following sets of actions:

- If FDA determines that the submission is sufficiently complete, FDA will file the sponsor's 586A request, notify the sponsor in writing that the request has been filed, and make the notification publicly available.[16]

[12] Section 586C of the FD&C Act (21 U.S.C. 360fff-3).

[13] Section 586B(a) of the FD&C Act (21 U.S.C. 360fff-2(a)).

[14] We note that section 586F(a)(1)(B) of the FD&C Act (21 U.S.C. 360fff-6) provides the possibility that sponsors of non-sunscreen TEAs submitted prior to enactment of the SIA may choose a review framework that would incorporate "an initial filing review under the processes and procedures described in section 586B(b)." FDA expects to conduct initial filing reviews for such applications in the same manner as 586A requests for sunscreen active ingredients.

[15] Section 586C(a)(1) of the FD&C Act (21 U.S.C. 360 fff-3(a)(1)).

[16] Section 586B(b)(2)(A) of the FD&C Act (21 U.S.C. 360fff-2(b)(2)(A)).

- If FDA determines that the submission is not sufficiently complete, FDA will refuse to file the sponsor's 586A request and GRASE data submission, notify the sponsor in writing of the determination to refuse to file the request, and make the notification publicly available. The notification will explain the reasons for the refusal, including why the GRASE submission was not sufficiently complete.[17]

If FDA refuses to file the sponsor's request, the sponsor may, within 30 days of receipt of the notification, request in writing a meeting with FDA to discuss the refusal to file.[18] The sponsor may also submit additional data or other information to FDA. If the sponsor requests a meeting, FDA will convene that meeting within 30 days of the request.[19] Following such a meeting, FDA may file the request within 60 days, the sponsor may submit additional data or other information, or the sponsor may, within 120 days, direct FDA to file the request over protest, with or without amendments to correct any deficiencies in the request.[20] If the sponsor submits additional data or other information (whether before, after, or in the absence of a meeting), FDA must reconsider its initial refusal to file, along with any additional information provided by the sponsor, and make a new filing determination within 60 days.[21] If, after a meeting, the sponsor elects to have FDA file the request, FDA will file the request over protest within 30 days of the sponsor's election, notify the sponsor in writing that the request has been filed, and make such notification public.[22]

C. Scope of This Draft Guidance

This draft guidance describes our current thinking on the content and format of a complete and fileable request under the SIA. When final, the recommendations in this draft guidance will provide advice to sponsors on how to prepare a successful GRASE submission, as well as guide FDA's filing determinations.

As noted in section II.B above, the "refusal to file" provision in the SIA applies only to GRASE data submissions made by sponsors to support 586A requests.[23] However, we anticipate that the advice in this draft guidance will also be useful to persons who are preparing safety and efficacy data submissions for review by FDA in other regulatory proceedings whose intent is to determine whether particular nonprescription drug active ingredients or other OTC conditions are GRASE

[17] Section 586B(b)(2)(B) of the FD&C Act (21 U.S.C. 360fff-2(b)(2)(B)).

[18] Section 586B(b)(3) of the FD&C Act (21 U.S.C. 360fff-2(B)(b)(3)).

[19] Section 586B(b)(3)(B) of the FD&C Act (21 U.S.C. 360fff-2(B)(b)(3)(B)).

[20] Section 586B(b)(3).

[21] Section 586B(b)(3)(C) of the FD&C Act (21 U.S.C. 360fff-2(b)(3)(C)).

[22] Section 586B(b)(3)(B)(ii)((III) of the FD&C Act (21 U.S.C. 360fff-2(b)(3)(B)(ii)(III)).

[23] As previously noted, non-sponsors also may submit partial or supplemental information and views to the applicable public docket (such as scientific articles, professional opinions, or statements from public advocacy groups). While such submissions are not subject to filing review, we recommend that interested parties consult the recommendations in this draft guidance to the extent that they are applicable to a given submission.

and therefore may be included in an applicable OTC monograph (such as a future non-sunscreen TEA request or a request for additional data in an ongoing SIA proceeding).

This draft guidance does not detail the specific clinical and nonclinical data that should be submitted to support a GRASE determination for a nonprescription sunscreen active ingredient. Instead, it broadly identifies the key structural elements, topics to be addressed, and recommended organization of a complete and fileable GRASE data submission. For the Agency's current thinking on the specific scientific testing and data recommended to support a GRASE determination for sunscreen active ingredients, see the guidance *Over-the-Counter Sunscreens: Safety and Effectiveness Data* (Safety and Effectiveness Draft Guidance). Sponsors are encouraged to read that draft guidance document and meet with FDA before preparing and submitting a GRASE data submission.

D. Related Draft Guidance

In addition to this draft guidance, the SIA directs FDA to issue three additional draft guidance documents on other topics.[24] These topics include:

- The data required to meet the safety and efficacy standard for determining whether a nonprescription sunscreen active ingredient is GRASE and not misbranded (the Safety and Efficacy Draft Guidance)

- The process for withdrawing a 586A request or a pending request

- The process by which FDA will carry out section 586C(c) of the FD&C Act as amended by the SIA, including the process for requesting an advisory committee meeting, the circumstances that limit the number and frequency of advisory committee meetings FDA is required to convene, and the number of requests to be considered per advisory committee meeting.

As they become available, FDA will make these draft guidances available on the FDA Drugs guidance Web page.[25]

III. CHARACTERISTICS OF A COMPLETE GRASE DATA SUBMISSION

A. General Recommendations

[24] Section 586D(a)(1)(A) of the FD&C Act (21 U.S.C. 360fff-4(a)(1)(A)); see also "Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2015," available online at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf.

[25] When available, FDA will post each draft guidance on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, these guidances will represent the FDA's current thinking on these topics.

FDA will refuse to file 586A requests for which the data and other information submitted are not sufficiently complete. GRASE data submissions that are materially incomplete or inadequately formatted do not permit FDA to conduct a substantive review. A complete submission by the sponsor should generally have the following characteristics:

1. A separate submission should be provided for each active ingredient that is the subject of a 586A request.

2. All data and information relevant to the requested GRASE determination should be provided in a single submission. A complete GRASE submission should include all of the data on which the sponsor intends to rely.[26]

3. If the sponsor wants FDA to consider data or information previously provided to FDA (such as data submitted to an NDA or ANDA, to the OTC sunscreen monograph proceeding, to another SIA docket, or in a citizen petition, the submission should identify the prior submission, submission date, and docket number and provide a complete copy of the previously submitted information.

4. If the submission refers to a literature search or searches, the submission should identify the databases included in each search and the search terms used. The submission should include complete copies of scientific articles or other published materials that the sponsor wishes FDA to consider as part of its review. Each literature search should be placed (by subject) in the appropriate section of the submission, as described in section III.B of this draft guidance. Copies of scientific articles and other published materials should also be placed in the relevant sections by subject. For electronic submissions, all items in reference lists and all in-text references citing scientific articles or other published materials should include a hyperlink to a full copy of the referenced article or other published material. If the submission is not electronic, each item in the reference list and all in-text references should provide specific location data for the full copy of the referenced material.

5. The submission should be in the English language. If any portion of a submission is in a foreign language, the sponsor should provide a complete and accurate English translation.

6. The SIA requires that any information included in a GRASE data submission that the sponsor considers to be confidential must be identified by the sponsor at the time of the

[26] The recommendations in this draft guidance are primarily directed to sponsors who are preparing a complete safety and efficacy data submission. Once such a submission has been made, sponsors should limit any further (supplemental) submissions to important, newly acquired data (such as safety data or results of newly completed or newly published studies). A supplemental submission should identify the original submission and the original submission date and should be labeled as a supplement.

Depending on the volume and complexity of a supplemental submission and when it is submitted, it may be difficult or impossible for FDA to conduct a thorough scientific review within the stringent timelines prescribed by the SIA. Nonetheless, FDA encourages the submission of important new adverse safety information at any time during the review process.

submission.[27] The sponsor might also consider redacting information that is not relevant to a GRASE determination, such as:

- Contractual relationships that are not public (e.g., names of contract testing laboratories or raw material suppliers) and names of contractors' employees.

- The names of employees of the sponsor or its contractors, such as technicians, nurses, or sub-investigators.

- Product formulation information that is not public and is not relevant to a GRASE determination (e.g., quantity of an inactive ingredient).

7. Safety and efficacy data that are not available to the public cannot be relied on to support a conclusion that an active ingredient is *generally recognized* as safe and effective. Accordingly, **sponsors should not submit, and FDA generally does not intend to rely on, evidence of safety and efficacy that the sponsor has marked as confidential** unless the sponsor also includes a statement that the information may be released to the public. Similarly, if the submission includes data or information marked as confidential by a third party (such as a contract research organization or consultant), the sponsor should include a statement that the sponsor is authorized to make the information publicly available or include an authorization from the third party permitting the information to be publicly disclosed. If a data submission includes studies or other information that were previously submitted to an NDA or ANDA submission without marking them as confidential, FDA intends to presume that the sponsor intends to make such data publicly available.

The principle that data to support a GRASE determination must be publicly available is most pertinent to studies or detailed study findings that are critical to FDA's evaluation of safety and efficacy, such as information needed to confirm that the study was appropriately designed and conducted or detailed study findings needed to substantiate the reported study results. This principle does not apply to information that has no bearing on FDA's scientific review of safety and efficacy data, such as that described in item 6, because such information is not relevant to a GRASE determination.

To enable a timely filing review, Module 1[28] should include the following, under the heading "Confidential Information":

- A statement that all information considered by the sponsor to be confidential has been identified in the data submission, with a description of the method used to designate the information as confidential

- A statement identifying any confidential study or report, or a significant portion of it, that may not be released to the public or that lacks required third-party permission for public

[27] Section 586B(b)(4) of the FD&C Act (21 U.S.C. 360fff-2(b)(4)).

[28] For more information on Module 1, see section III.B.

release. For purposes of this statement, FDA considers a portion to be significant if it is important to permit a full evaluation of study methods and conclusions

8. All pages should be numbered.

9. FDA encourages electronic submissions.

B. Recommended Organization and Contents

FDA recommends that the GRASE data submission be organized using the general structure and table of contents (TOC) described in the Common Technical Document (CTD) in effect at the time of the submission.[29] The CTD is an internationally harmonized set of specifications for preparing applications relating to new drugs that is maintained by the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use and has been recommended by the FDA in multiple guidance documents. Using this organized approach will streamline FDA's GRASE review because the CTD format is familiar to and routinely used by FDA's subject matter reviewers.

A submission using the eCTD TOC should be organized into five modules:

1. Administrative Information
2. Overview and Summary of Modules 3 to 5
3. Relevant Quality Information
4. Preclinical Data (Pharmacology/Toxicology)
5. Clinical Safety and Efficacy

The TOC in a GRASE data submission should be detailed, including both major section headings and subheadings. However, **it is neither necessary nor recommended that GRASE data submissions meet the full technical specifications of an eCTD or include all of the information identified in the CTD TOC headings**. Because the eCTD TOC is designed to accommodate *multiple* types of regulatory applications, it contains many headings and subheadings that are not pertinent to the safety and efficacy of these ingredients. We therefore do not recommend that such information be included in a GRASE data submission. However, we do recommend that your TOC include all of the major headings from the CTD TOC (using the appropriate heading numbers) and indicate, when appropriate, that no information is being submitted for a given heading.

If the submission is electronic, the TOC should include hyperlinks to each section. If a submission is not electronic, the submission should still be organized using the eCTD TOC.

A complete GRASE data submission based on the eCTD TOC should generally have the following characteristics:

[29] Current ICH and FDA guidances use the term "eCTD" (or electronic CTD) rather than "CTD" to reflect the transition to mandatory electronic submissions for regulatory submissions other than the GRASE data submissions addressed in this draft guidance.

MODULE 1: ADMINISTRATIVE INFORMATION

- Include any administrative and labeling information.

- Include statements about confidential information recommended in item 7 of section III.A.

- Include a cover letter that identifies the type of submission, the sponsor, the full contact information for the sponsor, the submission date, the active ingredient that is the subject of the submission, and the applicable docket number.

- Include any financial disclosure information, if applicable.

MODULE 2: SUMMARIES

- Overall Summary: Include a concise narrative summary of (1) the evidence supporting a conclusion that the active ingredient is GRASE for the intended nonprescription use and (2) the data that are not supportive of a determination that the active ingredient is GRASE. The summary should clearly identify and address each of the major topics addressed in the submission.

  Also include a summary table listing all studies relied upon in the submission with their corresponding titles (as they appear in the study reports), study numbers, and location in the submission (with hyperlinks to each study if the submission is submitted electronically). There should be one clearly identified study number for each study submitted.

- Overall Quality Summary: Include a summary of all chemistry, manufacturing, and controls data included in the submission.

- Nonclinical Summary: Include a narrative summary of all nonclinical data included in the submission. This summary should address data that are both supportive and non-supportive of a determination that the ingredient is GRASE.

- Clinical Summary: Include a narrative summary of all clinical data included in the submission. This summary should address data that are both supportive and non-supportive of a determination that the active ingredient is GRASE.

MODULE 3: QUALITY DATA

- Compendial Status: Include the compendial status of the active ingredient(s), including the current status of the United States Pharmacopeia (USP) listing(s) application.

- Chemical and/or Manufacturing Characteristics: Include any known chemical and/or manufacturing characteristics of the active ingredient that may be relevant to FDA's GRASE evaluation. For example, include known interactions with other sunscreen active ingredients or commonly used sunscreen vehicle components; specific requirements for formulation that enhance photostability, efficacy or safety; or information on particle size for micronized or nanoscale active ingredients.

MODULE 4: NONCLINICAL STUDY REPORTS

This module should include data and reports from nonclinical studies discussed in the Safety and Efficacy Draft Guidance, as well as any other types of nonclinical information (e.g., literature searches, scientific articles, or other published materials). Full copies of all published materials should be provided. The specific ingredient and formulation(s) used in each study should be described in detail.

Each individual study in the submission should include its own TOC and summary. Complete data sets (not selected or summary data) should be included in the submission. We expect that data from studies provided only in summary form will generally not be considered sufficient evidence that an active ingredient is GRASE.

Examples of nonclinical studies to be provided in this module include dermal and systemic carcinogenicity studies, developmental and reproductive toxicity studies, and animal toxicokinetic data.

MODULE 5: CLINICAL STUDY REPORTS

Module 5 should include separate comprehensive integrated summaries of effectiveness and clinical safety. The summary of effectiveness should include the active ingredient's mechanism of action and the specific doses, concentrations, and formulations proposed for use. The summary of safety should include exposure data, and, if available, address safety in specific populations such as children, the elderly, and pregnant or lactating women. The summary of safety should also address specific safety issues expected with either the ingredient or its application. For sunscreens, examples of such safety issues could include dermal safety, hypersensitivity, accidental ocular exposure, or inhalational safety. All available efficacy and safety data, including both supportive data and any data demonstrating potential safety signals, should be submitted.

This module should also include full reports of (1) all clinical effectiveness and safety studies and other clinical data and (2) all clinical pharmacology and human toxicokinetic data. In addition to actual study reports, all other types of clinical data (e.g., from literature searches, scientific articles, or other published materials) should be included in this module. Full copies of all published materials should be provided. Each study report should contain a description of the specific ingredient and formulation(s) used. For literature reports, this information may be included in the relevant summary document.

Human studies to be included in Module 5 are discussed in the Safety and Effectiveness Data Draft Guidance. These include sun protection factor studies and other effectiveness studies (such as in vitro broad spectrum studies, if performed), human irritation and sensitization studies, human photosafety studies, human absorption studies, and human maximal usage trials.

Module 5 should also include reports of in vitro testing performed by the sponsor in connection with human maximal usage trials to support final formulation safety testing if the active ingredient is determined to be GRASE, as discussed in Safety and Effectiveness Data Draft Guidance.

Each individual study in the submission should include its own TOC and summary. Complete data sets (not selected or summary data) should be included in the submission. Generally, we intend not to consider study data provided only in summary form to be sufficient evidence that an active ingredient is GRASE.

Further, postmarketing safety data as discussed in the Safety and Effectiveness Data Draft Guidance,[30] should be included in Module 5. For adverse event reports, there should be a TOC with a separate link to each adverse event report. The section on adverse event reports should be organized according to the Medical Dictionary for Regulatory Activities System Organ Class categories.

C. Characteristics of an Incomplete Request and GRASE Data Submission

Some examples of incomplete information or inadequate organization that may render the GRASE data submission insufficiently complete[31] for review are listed below.[32] These characteristics could cause FDA to refuse to file a GRASE data submission.

1. The submission is unreasonably disorganized—that is, its structure does not permit ready review for completeness by lacking a recommended TOC that itemizes the submission's elements and data.

2. Electronic submissions cannot be opened or readily navigated (e.g., hyperlinks do not operate).

3. Data tabulations or graphic displays are not interpretable, are inadequately labeled, or do not indicate data sources.

4. Summaries or tables of contents do not indicate or link to the location of specific discussions, studies, or other referenced information elsewhere in the submission.

[30] Id.

[31] See section 586B(b)(2) of the FD&C Act.

[32] Please note that this list is not exhaustive.

5. The submission is materially incomplete on its face (e.g., it does not include sufficient information for FDA to make a GRASE determination because it completely fails to include some or all of the information identified in Section III.B of this draft guidance, unless the sponsor explains the reasons why the missing information is not included and why the active ingredient or other condition should be found to be GRASE in its absence).

6. All or essential portions of the submission are marked as confidential.

D. How and Where To Submit GRASE Data Submissions

GRASE data submissions can be sent (1) in hard copy to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 or (2) electronically to http://www.regulations.gov using the previously established docket number. In addition, a copy of the cover letter should be sent to the Division of Nonprescription Drug Products, Food and Drug Administration, Bldg. 22, Mail Stop 5411, 10903 New Hampshire Avenue, Silver Spring, MD 20993.